

Claims

1. A compound of formula (I)

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wherein:

A is 5- or 6-membered monocyclic aromatic ring containing 1, 2 or 3 ring heteroatoms

10 selected from nitrogen, oxygen and sulphur atoms optionally substituted by one, two or three atoms or groups selected from halo, oxo, carboxy, trifluoromethyl, cyano, amino, hydroxy, nitro, C<sub>1-4</sub>alkyl (for example methyl or ethyl), C<sub>1-4</sub>alkoxy (for example methoxy or ethoxy), C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>alkylamino (for example methylamino or ethylamino) or di-C<sub>1-4</sub>alkylamino (for example dimethylamino or diethylamino);

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B is a phenylene ring optionally substituted by one or two substituents selected from halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl and C<sub>2-4</sub>alkynyl, from the substituent -(CH<sub>2</sub>)<sub>n</sub>Y<sup>1</sup> wherein n is 0-4 and Y<sup>1</sup> is selected from hydroxy, amino, carboxy, C<sub>1-4</sub>alkoxy, C<sub>2-4</sub>alkenyloxy, C<sub>2-4</sub>alkynyloxy, C<sub>1-4</sub>alkylamino, di-C<sub>1-4</sub>alkylamino, pyrrolidin-20 1-yl, piperidino, morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, piperazin-1-yl, 4-C<sub>1-4</sub>alkylpiperazin-1-yl, C<sub>1-4</sub>alkylthio, C<sub>1-4</sub>alkylsulphiny, C<sub>1-4</sub>alkylsulphonyl, C<sub>2-4</sub>alkanoylamino, benzamido, C<sub>1-4</sub>alkylsulphonamido and phenylsulphonamido, from the substituent -(CH<sub>2</sub>)<sub>n</sub>Y<sup>2</sup> wherein n is 0-4 and Y<sup>2</sup> is selected from carboxy, carbamoyl, C<sub>1-4</sub>alkoxycarbonyl, N-C<sub>1-4</sub>alkylcarbamoyl, N,N-di-C<sub>1-</sub>

25 4alkylcarbamoyl, pyrrolidin-1-ylcarbonyl, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl,

1-oxothiomorpholinocarbonyl, 1,1-dioxothiomorpholinocarbonyl, piperazin-1-ylcarbonyl, 4-C<sub>1-4</sub>alkylpiperazin-1-ylcarbonyl, C<sub>1-4</sub>alkylsulphonamidocarbonyl,

phenylsulphonamidocarbonyl and benzylsulphonamidocarbonyl, from a substituent of the

30 formula -X<sup>3</sup>-L<sup>2</sup>-Y<sup>3</sup> wherein X<sup>3</sup> is a group of the formula CON(R<sup>3</sup>), CON(L<sup>2</sup>-Y<sup>2</sup>), C(R<sup>5</sup>)<sub>2</sub>O, O, N(R<sup>5</sup>) or N(L<sup>2</sup>-Y<sup>2</sup>), L<sup>2</sup> is C<sub>1-4</sub>alkylene, Y<sup>2</sup> has any of the meanings defined immediately hereinbefore and each R<sup>3</sup> is independently hydrogen or C<sub>1-4</sub>alkyl, and from a substituent of the formula -X<sup>3</sup>-L<sup>3</sup>-Y<sup>1</sup> wherein X<sup>3</sup> is a group of the formula CON(R<sup>3</sup>), CON(L<sup>3</sup>-Y<sup>1</sup>), C(R<sup>5</sup>)<sub>2</sub>O,

O, N(R<sup>3</sup>) or N(L<sup>3</sup>-Y<sup>1</sup>), L<sup>3</sup> is C<sub>2-4</sub>alkylene, Y<sup>1</sup> has any of the meanings defined immediately hereinbefore and each R<sup>3</sup> is independently hydrogen or C<sub>1-4</sub>alkyl, and wherein any heterocyclic group in a substituent of B optionally bears 1 or 2 substituents selected from carboxy, carbamoyl, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxycarbonyl, N-C<sub>1-4</sub>alkylcarbamoyl and

5 N,N-di-C<sub>1-4</sub>alkylcarbamoyl, and wherein any phenyl group in a substituent of B optionally bears 1 or 2 substituents selected from halo, trifluoromethyl, cyano, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl,

C<sub>1-4</sub>alkoxy, C<sub>2-4</sub>alkenyloxy and C<sub>2-4</sub>alkynyloxy;

T<sup>1</sup> is CH or N;

10 T<sup>2</sup> is CH or N;

with the proviso that at least one of T<sup>1</sup> and T<sup>2</sup> is N and wherein the heterocyclic ring formed by T<sup>1</sup>, T<sup>2</sup>, L<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> is optionally substituted by one or two substituents selected from hydroxy, oxo, carboxy and C<sub>1-4</sub>alkoxycarbonyl; or one of the following:

15 -(CH<sub>2</sub>)<sub>n</sub>-R, -(CH<sub>2</sub>)<sub>n</sub>-NRR<sup>1</sup>, -CO-R, -CO-NRR<sup>1</sup>, -(CH<sub>2</sub>)<sub>n</sub>-CO-R and -(CH<sub>2</sub>)<sub>n</sub>-CO-NRR<sup>1</sup>;

wherein n is 0, 1 or 2, preferably n is 1 or 2;

R and R<sup>1</sup> are independently selected from hydrogen, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, hydroxyC<sub>1-4</sub>alkyl, carboxyC<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxycarbonylC<sub>1-4</sub>alkyl or where possible R

20 and R<sup>1</sup> may together form a 5- or 6-membered optionally substituted saturated or partially unsaturated (preferably saturated) heterocyclic ring which may include in addition to the nitrogen to which R and R<sup>1</sup> are attached 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur

X<sup>1</sup> is SO, SO<sub>2</sub>, C(R<sup>4</sup>)<sub>2</sub> or CO when T<sup>1</sup> is CH or N; or in addition X<sup>1</sup> is O or S when T<sup>1</sup> is CH;

25 and wherein each R<sup>4</sup> is independently hydrogen or C<sub>1-4</sub>alkyl;

L<sup>1</sup> is C<sub>1-4</sub>alkylene or C<sub>1-3</sub>alkylenecarbonyl;

R<sup>2</sup> is hydrogen or C<sub>1-4</sub>alkyl;

R<sup>3</sup> is hydrogen or C<sub>1-4</sub>alkyl;

or R<sup>2</sup> and R<sup>3</sup> are joined to form a C<sub>1-4</sub>alkylene or -CH<sub>2</sub>CO- group; wherein the ring formed by

30 T<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, T<sup>2</sup> and L<sup>1</sup> is optionally substituted; with the proviso that when T<sup>1</sup> and T<sup>2</sup> are both N, L<sup>1</sup> is not methylene and R<sup>2</sup> and R<sup>3</sup> together are not methylene;

$X^2$  is  $S(O)_y$ , wherein  $y$  is one or two,  $C(R^3)_2$  or  $CO$ ; and each  $R^3$  is hydrogen or  $C_{1-4}$ alkyl;

$Q$  is phenyl, naphthyl, phenyl $C_{1-4}$ alkyl, phenyl $C_{2-4}$ alkenyl, phenyl $C_{2-4}$ alkynyl or a heterocyclic moiety containing up to 4 heteroatoms selected from nitrogen, oxygen and sulphur and  $Q$  is optionally substituted by one, two or three substituents selected from halo, trifluoromethyl,

- 5 trifluoromethoxy, cyano, hydroxy, amino, nitro, trifluoromethylsulphonyl, carboxy, carbamoyl,  $C_{1-4}$ alkyl,  $C_{2-4}$ alkenyl,  $C_{2-4}$ alkynyl,  $C_{1-4}$ alkoxy,  $C_{2-4}$ alkenyloxy,  $C_{2-4}$ alkynyloxy,  $C_{1-4}$ alkylthio,  $C_{1-4}$ alkylsulphinyl,  $C_{1-4}$ alkylsulphonyl,  $C_{1-4}$ alkylamino, di- $C_{1-4}$ alkylamino,  $C_{1-4}$ alkoxycarbonyl,  $N$ - $C_{1-4}$ alkylcarbamoyl,  $N,N$ -di- $C_{1-4}$ alkylcarbamoyl,  $C_{2-4}$ alkanoyl,  $C_{2-4}$ alkanoylamino, hydroxy $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl, carboxy $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxycarbonyl $C_{1-4}$ alkyl, carbamoyl $C_{1-4}$ alkyl,  $N$ - $C_{1-4}$ alkylcarbamoyl $C_{1-4}$ alkyl,  $N,N$ -di- $C_{1-4}$ alkylcarbamoyl $C_{1-4}$ alkyl, phenyl, heteroaryl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, benzyl, benzoyl, heteroaryloxy, heteroarylthio, heteroarylsulphinyl and heteroarylsulphonyl, and wherein said heteroaryl substituent or the heteroaryl group in a heteroaryl-containing substituent is a 5- or 6-membered monocyclic heteroaryl ring containing
- 10 up to 3 heteroatoms selected from nitrogen, oxygen and sulphur, and wherein said phenyl, heteroaryl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, heteroaryloxy, heteroarylthio, heteroarylsulphinyl, heteroarylsulphonyl, benzyl or benzoyl substituent optionally bears 1, 2 or 3 substituents selected from halo, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkylamino, di- $C_{1-4}$ alkylamino,  $C_{1-4}$ alkoxycarbonyl,  $N$ - $C_{1-4}$ alkylcarbamoyl,  $N,N$ -di- $C_{1-4}$ alkylcarbamoyl and  $C_{2-4}$ alkanoylamino;
- 20 and pharmaceutically acceptable salts thereof.

2. A compound of formula (I) according to claim 1 wherein  $A$  is a pyridyl, pyrimidinyl or pyridazinyl ring.

3. A compound of formula (I) according to claim 2 wherein  $A$  is 4-pyrimidinyl or 4-pyridyl.

4. A compound of formula (I) according to any one of claims 1 to 3 wherein  $B$  is paraphenylene.

5. A compound of formula (I) according to any one of claims 1 to 4 wherein the ring formed by T<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, T<sup>2</sup> and L is 1,4-piperazinediyl.

5 6. A compound of formula (I) according to any one of claims 1 to 5 wherein X<sup>1</sup> is CO.

7. A compound of formula (I) according to any one of claims 1 to 6 wherein X<sup>2</sup> is SO<sub>2</sub>.

8. A compound of formula (I), as defined in claim 1, wherein

10 A is pyridyl, pyrimidinyl, or pyridazinyl;

B is para-phenylene;

X<sup>1</sup> is CO, SO<sub>2</sub> or CH<sub>2</sub>;

T<sup>1</sup> and T<sup>2</sup> are both N;

L<sup>1</sup> is ethylene or propylene;

15 R<sup>2</sup> and R<sup>3</sup> are joined to form an ethylene or propylene or methylenecarbonyl group;

X<sup>2</sup> is SO<sub>2</sub>;

Q is styryl or naphthyl optionally substituted by fluoro, chloro or bromo or is phenyl optionally substituted by fluorophenyl, chlorophenyl, or bromophenyl; and pharmaceutically-acceptable salts thereof.

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9. A compound of formula (I) selected from:

1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(4-pyrimidinyl)benzoyl]piperazine;

1-(6-chloronaphth-2-ylsulphonyl)-4-[4-(4-pyridyl)benzoyl]piperazine;

1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(4-pyridazinyl)benzoyl]piperazine;

25 and pharmaceutically-acceptable salts thereof.

10. A compound of formula (I) according to any one of claims 1 to 9 for use in medical therapy.

30 11. A pharmaceutical formulation comprising a compound of formula (I) according to any one of claims 1 to 9 and a pharmaceutically-acceptable diluent or carrier.

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12. Use of a compound of formula (I) according to any one of claims 1 to 9 in the preparation of a medicament for use in producing a Factor Xa inhibiting effect.

13. A method of preventing or treating a Factor Xa mediated disease or medical condition comprising administering to a patient a pharmaceutically effective amount of a compound of formula (I), as defined in any one of claims 1 to 9.

14. A process for preparing a compound of formula (I), are defined in claim 1,  
comprising:

(a) for the production of those compounds of the formula (I) wherein  $T^1$  is N and  $X^1$  is CO, the reaction, conveniently in the presence of a suitable base, of an amine of formula (II)

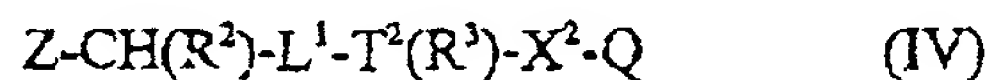


with an acid of the formula (III)



or a reactive derivative thereof;

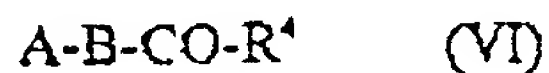
(b) for the production of those compounds of the formula (I) wherein  $T^1$  is CH and  $X^1$  is O by the reaction, conveniently in the presence of a suitable coupling agent, of a compound of the formula (IV):



wherein Z is a displaceable group, with a phenolic compound of the formula (V):



(c) for the production of those compounds of the formula (I) wherein  $T^1$  is N and  $X^1$  is  $CH(R^4)$ , the reductive amination of a keto compound of the formula (VI):

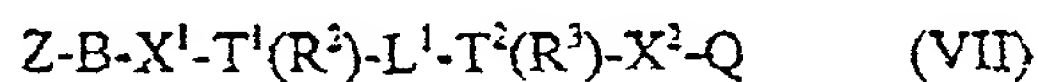


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wherein  $R^4$  is hydrogen or  $C_{1-4}$  alkyl, with an amine of the formula (II) as defined above;

(d) the reaction of a compound of the formula (VII):

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wherein Z is a displaceable group with an activated derivative of ring A;

(e) by forming A ring on compounds of formula (VII), wherein Z is a functional group  
15 capable of cyclisation;

(f) for the production of compounds wherein  $T^2$  is N, the reaction of a compound of the formula (VIII):

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with a compound of the formula (IX):

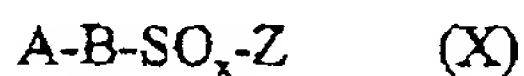


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wherein Z is a displaceable group;

(g) for the production of compounds wherein  $T^1$  is N and  $X^1$  is SO or  $SO_2$ , the reaction  
of a compound of the formula (II) as defined above with a compound of the formula (X):

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wherein x is one or two and Z is a displaceable group;

(h) for production of compounds of formula (I) by coupling T<sup>2</sup> to Q and thus preparing  
5 the -T<sup>2</sup>-X<sup>2</sup>-Q moiety, methods analogous to those described in process variants (a), (c) and (g)  
for preparing the B-X<sup>1</sup>-T<sup>1</sup>- moiety may be employed;

(i) for the production of compounds of formula (I) wherein X<sup>1</sup> is a group of the  
formula SO, SO<sub>2</sub>, wherein B bears a C<sub>1-4</sub>alkylsulphinyl, C<sub>1-4</sub>alkylsulphonyl,  
10 1-oxothiomorpholino or 1,1-dioxothiomorpholino group, wherein X<sup>2</sup> is a group of the formula  
SO or SO<sub>2</sub> wherein Q bears a C<sub>1-4</sub>alkylsulphinyl, C<sub>1-4</sub>alkylsulphonyl, phenylsulphinyl,  
phenylsulphonyl, heteroarylsulphinyl or heteroarylsulphonyl group, the oxidation of the  
corresponding compound of the formula (I) which contains X<sup>1</sup> as a thio group.